NELL-1 Injection Maintains Long Bone Quantity and Quality in an Ovariectomy-Induced Osteoporotic Senile Rat Model.

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Public Summary:
Over 10 million Americans have osteoporosis, and is the predominant cause of fractures in the elderly. Treatment of fractures in the setting of osteoporosis is complicated by a suboptimal bone regenerative response due to a decline in the number of osteoblasts, their function, and survival. Consequently, an osteogenic therapeutic to prevent and treat fractures in patients with osteoporosis is needed. Nel-like molecule-1 (NELL-1), a novel osteoinductive growth factor, has been shown to promote bone regeneration. In this study, we aim to demonstrate the capacity of recombinant NELL-1 to prevent ovariectomy (OVX)-induced osteoporosis in a senile rat model. Ten-month-old female Sprague-Dawley rats underwent either sham surgery or OVX. Subsequently, 50 µL of 600 µg/mL NELL-1 lyophilized onto a 0-50-µm tricalcium phosphate (TCP) carrier was injected into the femoral bone marrow cavity while phosphate-buffered saline (PBS) control was injected into the contralateral femur. Our microcomputed tomography results showed that OVX+PBS/TCP control femurs showed a continuous decrease in the bone volume (BV) and bone mineral density (BMD) from 2 to 8 weeks post-OVX. In contrast, OVX+NELL-1/TCP femurs showed resistance to OVX-induced bone resorption showing BV and BMD levels similar to that of SHAM femurs at 8 weeks post-OVX. Histology showed increased endosteal-woven bone, as well as decreased adipocytes in the bone marrow of NELL-1-treated femurs compared to control. NELL-1-treated femurs also showed increased immunostaining for bone differentiation markers osteopontin and osteocalcin. These findings were validated in vitro, in which addition of NELL-1 in OVX bone marrow stem cells resulted in increased osteogenic differentiation. Thus, NELL-1 effectively enhances in situ osteogenesis in the bone marrow, making it potentially useful in the prevention and treatment of osteoporotic fractures.

Scientific Abstract:
Over 10 million Americans have osteoporosis, and is the predominant cause of fractures in the elderly. Treatment of fractures in the setting of osteoporosis is complicated by a suboptimal bone regenerative response due to a decline in the number of osteoblasts, their function and survival. Consequently, an osteogenic therapeutic to prevent and treat fractures in osteoporotic patients is needed. NELL-1 (Nel-like molecule-1), a novel osteoinductive growth factor, has been shown to promote bone regeneration. In this study, we aim to demonstrate the capacity of recombinant NELL-1 to prevent ovariectomy (OVX)-induced osteoporosis in a senile rat model. Ten month old female Sprague Dawley rats underwent either sham surgery or OVX. Subsequently, 50 uL of 600 ug/ml NELL-1 lyophilized onto 0-50 um tricalcium phosphate (TCP) carrier was injected into the femoral bone marrow cavity while phosphate buffered saline (PBS) control was injected into the contralateral femur. Our microCT results showed that OVX+PBS/TCP control femurs showed a continuous decrease in bone volume (BV) and bone mineral density (BMD) from 2 to 8 weeks post-OVX. In contrast, OVX+NELL-1/TCP femurs showed resistance to OVX-induced bone resorption showing BV and BMD levels similar to that of SHAM femurs at 8 weeks post-OVX. Histology showed increased endosteal woven bone, as well as decreased adipocytes in the bone marrow of NELL-1 treated femurs compared to control. NELL-1 treated femurs also showed increased immunostaining for bone differentiation markers Osteopontin (OPN) and Osteocalcin (OCN). These findings were validated in vitro, in which addition of NELL-1 in OVX bone marrow stem cells resulted in increased osteogenic differentiation. Thus, NELL-1 effectively enhances in situ osteogenesis in the bone marrow, making it potentially useful in the prevention and treatment of osteoporotic fractures.